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10/590,678	06/04/2007	**Frank Karlsen**	B0192.70065US00	2839

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,678	KARLSEN, FRANK	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☒ Claim(s) *11,20 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/2008; 8/6/2007; 8/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 2 and 13-21, in the reply filed on October 20, 2009 is acknowledged. It is noted that the response does not indicate whether the election is made with or without traverse. Since Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However, upon further consideration, the restriction requirement mailed on July 21, 2009 has been **WITHDRAWN**. All of the pending claims (*i.e.* claims 1-30) will be examined on the merits.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on August 25, 2006, August 6, 2007, and October 7, 2008 is acknowledged. Signed copies are enclosed.

The copending applications and International Search Reports from related PCT applications listed on page 2 of the letter accompanying the IDS filed on October 7, 2008 have also been considered by the Examiner.

Non-patent literature citation C26 in the IDS filed on October 7, 2008 has been edited to include the year of the conference. Also, non-patent literature citation C12 in the IDS filed on October 7, 2008 has been corrected to recite the correct page numbers of the reference.

Claim Objections

4. Claims 11, 20, and 29 are objected to because of the following informalities: The meaning of the acronyms ASCUS and CIN 1 should be written out in the claims before use of the acronyms.

Claim Rejections - 35 USC § 112, 1st paragraph (Scope of Enablement)

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, and 13-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (i) an *in vitro* method of screening human subjects to assess their risk of having cervical cells that exhibit aneuploidy and enlarged nuclei as a result of HPV infection that comprises detecting the presence of mRNA transcripts of the E6/E7 gene from HPV-16, 18, 31, 33, or 45 that encode a full-length E6 protein in a cervical cell sample obtained from the subject, wherein the presence of the aforementioned transcripts in the sample is indicative of an increased risk of having cervical cells that exhibit aneuploidy and enlarged nuclei as a result of HPV infection, or (ii) an *in vitro* method for screening human subjects to assess their risk of having or developing a persistent transforming infection with HPV-16, 18, 31,

33, or 45 that comprises detecting the presence of mRNA transcripts of the E6/E7 gene from HPV-16, 18, 31, 33, or 45 that encode a full-length E6 protein in a cervical cell sample obtained from the subject, wherein the presence of the aforementioned transcripts in the sample is indicative of an increased risk of having or developing a persistent transforming infection with HPV-16, 18, 31, 33, or 45, does not reasonably provide enablement for an *in vitro* method for screening human subjects for the presence of any type of cellular changes characterized by cellular aneuploidy and enlarged cell nuclei based solely on the detection of mRNA transcripts of the E6/E7 gene from any type of HPV that encode a full-length E6 protein in a test sample obtained from a human subject or an *in vitro* method of screening human subjects for the presence of a persistent transforming infection with HPV based solely on the detection of mRNA transcripts of the E6/E7 gene from any type of HPV that encode a full-length E6 protein in a test sample obtained from a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention

The methods of the instant claims are classified in the unpredictable arts of biochemistry and molecular biology. The instant claims 2 and 13-21 are drawn to *in vitro* methods for screening human subjects for the presence of cellular changes characterized by enlarged cell nuclei or aneuploidy. The methods comprise analyzing a test sample obtained from the subject, for example, by real-time NASBA, to determine whether or not the test sample contains mRNA transcripts of an HPV E6/E7 gene that encode a full-length E6 protein, wherein the presence of E6/E7 transcripts encoding a full-length E6 protein are indicative of the aforementioned cellular changes. The instant claims 3 and 22-30 are drawn to *in vitro* methods for screening human subjects for the presence of a persistent transforming infection with HPV. The methods comprise analyzing a test sample obtained from the subject, for example, by real-time NASBA, to determine whether or not the test sample contains mRNA transcripts of an HPV E6/E7 gene that encode a full-length E6 protein, wherein the presence of E6/E7 transcripts encoding a full-length E6 protein are indicative the presence of a persistent transforming infection with HPV.

The breadth of the claims

The methods of claims 2 and 13-21 are extremely broad in scope. Claims 2, 13, and 16-18 encompasses correlating the presence of an E6/E7 mRNA transcript from any type of HPV (*i.e.,* high-risk HPV types, such as HPV-16, and low-risk HPV types, such as HPV-6) that encodes a full-length E6 protein in a test sample obtained from a human subject with the presence of any type of cellular changes characterized by enlarged cell nuclei or aneuploidy. The number of cellular changes falling within the scope of the claims is simply enormous and

includes any type of cancer, CIN lesions of any degree, ASCUS, condylomas, ectopic adrenocorticotropic hormone syndrome (see, for example, Li et al., Endocrine Pathology (1990) 1(3): 183-191), and ataxia-telangiectasia (see, for example, Cohen et al., Diagnostic Cytopathology (1997) 17(6): 484-486). Claims 14 and 15 further limit the type of HPV to HPV-16, 18, 31, 33, and 45. Claims 19-21 specify that: (i) the human subjects screened by the method have been diagnosed as having an HPV infection, (ii) the human subjects screened by the method have been previously diagnosed as having ASCUS, CIN-I lesions, or condyloma, and (iii) the human subjects screened by the method have not been diagnosed as having cervical abnormalities by cytology, respectively.

The methods of claims 3 and 22-30 are also very broad in scope. Claims 3, 22, and 25-27 encompasses correlating the presence of an E6/E7 mRNA transcript from any type of HPV (*i.e.,* high-risk HPV types, such as HPV-16, and low-risk HPV types, such as HPV-6) that encodes a full-length E6 protein in a test sample obtained from a human subject with the presence of a persistent transforming infection with HPV. The specification defines the term "persistent transforming infection" as being "equivalent to persistent cell abnormalities or persistent CIN-III lesions, cancer *in situ* or high-grade squamous intraepithelial lesions (HSIL) (see page 9, last paragraph - page 10, first paragraph). Thus, the term "persistent transforming infection" is not limited to HPV-linked cervical cancer or persistent CIN-III lesions, but broadly encompasses any type of persistent cell abnormalities. Claims 23 and 24 further limit the type of HPV to HPV-16, 18, 31, 33, and 45. Claims 28-30 specify that: (i) the human subjects screened by the method have been diagnosed as having an HPV infection, (ii) the human subjects screened by the method have been previously diagnosed as having ASCUS, CIN-I lesions, or condyloma, and (iii) the

human subjects screened by the method have not been diagnosed as having cervical abnormalities by cytology, respectively.

Guidance in the Specification and Working Examples

The specification teaches that detection of the presence of an E6/E7 mRNA transcript from HPV that encodes a full-length E6 protein in a test sample obtained from a human subject indicates that the subject has a persistent transforming infection with HPV and cellular abnormalities characterized by aneuploidy and enlarged cell nuclei (see pages 5-11). The specification also teaches that HPV-associated cervical cancer is limited to a small number of HPV types, including HPV-16, 18, 31, 33, and 45 (see pages 2 and 16, for example). The specification also teaches that HPV-associated cervical cancer, CIN lesions, and condylomas are associated with cellular abnormalities, such as aneuploidy and enlarged cell nuclei (see pages 9-10 and 12-13, for example).

The working examples describe studies conducted to assess the ability of mRNA transcripts from HPV to identify cellular abnormalities and persistent transforming HPV infections. Examples 1, 2, and 5 are particularly relevant to the claimed methods. Examples 1 and 2 relate to the correlation of cellular abnormalities with the presence of E6/E7 transcripts from HPV-16, 18, 31, 33, and 45 that encode a full-length E6 protein. Example 5 relates to the correlation of a persistent HPV infection with the presence of E6/E7 transcripts from HPV-16, 18, 31, 33, and 45 that encode a full-length E6 protein.

In Example 1, 4136 cervical samples classified by cytology as HGSIL/AGUS, HSIL/ASC-H, HGSIL/CIN2, or HGSIL/CIN3 were screened for the presence of E6/E7 mRNA

transcripts from HPV-16, 18, 31, 33, and 45 that encode full-length E6 proteins using multiplex real-time NASBA (pages 26-28). The results indicate that HPV-16, 18, 31, 33, and 45 E6/E7 transcripts that encode full-length E6 proteins were found in nearly all histological CIN2+ cases (page 27). The data in example 1 suggest that the detection of the aforementioned transcripts can be used to confirm histology results and/or to screen human subjects for an increased risk of having CIN2+ lesions.

In Example 2, cervical samples diagnosed by cytology as having ASCUS or CIN1 lesions were analyzed using a real-time multiplex NASBA assay that screens for the presence of E6/E7 transcripts from HPV 16, 18, 31, 33, and 45 that encode a full-length E6 protein at the time of cytological diagnosis and one year later (pages 28-31). Cytological and histological analysis was also performed after the original diagnosis. The results are similar to those of Example 1, in that the multiplex NASBA assay was capable of detecting nearly all histological CIN2+ cases that developed from the original ASCUS or CIN1 cells (pages 30-31).

In Example 5, 54 women diagnosed as positive for HPV-16, 18, 31, 33, or 45, but lacking cytological abnormalities, were screened two years later by multiplex real-time NASBA for the presence of E6/E7 transcripts from HPV-16, 18, 31, 33, and 45 encoding full-length E6 proteins and also by conventional cytological assays for the presence of cellular abnormalities (see pages 35-38). The results indicate that the presence of the aforementioned E6/E7 transcripts was more correlated with the development of cellular abnormalities.

However, neither the specification nor the working examples correlates the presence of E6/E7 mRNA transcripts encoding full-length E6 proteins from any HPV genotype other than HPV-16, 18, 31, 33, and 45 with the presence of: (a) cervical cancer or persistent CIN-III lesions

(*i.e.*, a persistent transforming HPV infection), or (b) cellular abnormalities, such as enlarged nuclei and aneuploidy. Also, neither the specification nor the working examples correlates the presence of E6/E7 mRNA transcripts encoding full-length E6 proteins from any HPV genotype with the presence of cellular changes characterized by aneuploidy and enlarged nuclei resulting from any other condition than HPV infection.

Quantity of Experimentation

The quantity of experimentation in this area is immense, since, as discussed below, there is a very high degree of unpredictability as to: (i) whether the presence of mRNA transcripts from the E6/E7 gene encoding a full-length E6 protein from any particular type of HPV other than HPV-16, 18, 31, 33, and 45 will be indicative of a human subject's risk of having or developing a persistent transforming infection with HPV, and (ii) whether the presence of mRNA transcripts from the E6/E7 gene encoding a full-length E6 protein from any particular type of HPV will be indicative of a human subject's risk of having cells characterized by aneuploidy and enlarged nuclei in a sample obtained from the subject.

As a result of this unpredictability inherent in the claimed methods, the ordinary artisan would be required to conduct an extensive amount of non-routine and unpredictable experimentation with essentially no guidance from the prior art or the instant application's specification and with no guarantee of success in order to practice the full scope of the claimed methods. Specifically, the ordinary artisan would have to establish, via the analysis of a large number of patients, that a the presence of transcripts encoding a full-length E6 protein from a particular type of HPV in a sample obtained from a human subject are indicative of a persistent

transforming infection in the subject. The ordinary artisan would also have to establish, again through analysis of a large number of patients, that the presence of transcripts encoding full-length E6 proteins from each particular type of HPV encompassed by the claims is indicative of each type of cellular change characterized by aneuploidy and enlarged nuclei. Given the breadth of the claims, each set of experiments would have to be conducted independently of each other, and would provide little guidance as to the other sets of experiments.

State of the Prior Art and Unpredictability in the Art

As discussed in greater detail below, the prior art of Nakagawa et al. (Journal of Medical Virology (2000) 62: 251-256; cited previously) and Karlsen et al. (WO 2003/057914 A2; cited on an IDS) teaches methods falling within the genus encompassed by the claimed methods. However, the prior art does not teach that the presence of transcripts encoding a full-length HPV E6 protein from any type of HPV is indicative of a persistent transforming infection with HPV. The prior art also does not indicate that the presence of transcripts encoding a full-length HPV E6 protein from any type of HPV is indicative of any type of cellular changes characterized by enlarged cell nuclei and aneuploidy.

The relationship between particular types of HPV and their association with the development of certain cancers has been extensively studied for many years. It is well documented in the art, as demonstrated by the review article of Anderson et al. (Clinical Microbology Newsletter (August 2002) 25(15):113-118; cited on an IDS), that only certain types HPV are associated with genital lesions (see Table 2, for example). Furthermore, it has been well established that only certain types of HPV that are associated with genital lesions also carry a

high-risk of cervical lesions and cancer (see Table 3, for example). Lastly, it has also been well established that high-risk HPV types can be distinguished from other HPV types based on the structure and function of the E6 gene product, because the E6 protein has a high affinity for the p53 host gene products (see page 115, for example). Thus, the art suggests that the detection of mRNA transcripts of the E6/E7 gene of HPV other than HPV-16, 18, 31, 33, or 45 is not an indication that the patient is at high-risk for the development of cervical cancer. Rather, the art suggests that the opposite is true.

The art further suggests that the detection of transcripts encoding a full-length E6 protein from any type of HPV is no way an indication that the patient definitively has abnormal cell changes, such as aneuploidy and enlarged cell nuclei or a persistent transforming infection with HPV, at the time of detection. For example, Anderson states that "[C]ervical cancer develops in a multi-step process that most often takes many years and involves both presence of oncogene HPV genotypes and the interaction of many host factors….Several studies have shown that persistent infection with oncogenic viral types, such as HPV 16, is a very important determinant in the development of cervical cancer (page 114, column 3 – page 115, column 1)." Thus, the art suggests that the detection of mRNA transcripts of the E6 gene of HPV-16, 18, 31, 33, or 45, while being an important factor in the diagnosis of cervical cancer, is in no way an indication that the patient definitively has abnormal cell changes at the time of detection. In fact, Example 5 on pages 35-37 specification appears to indicate that biopsies of a negative cytology, in some instances, actually showed oncogenic E6 mRNA expression. Furthermore, as noted above, the prior art does not indicate that the detection of mRNA transcripts of an HPV E6/E7 gene

encoding a full-length E6 protein are indicative of any cell change characterized by enlarged cell nuclei and aneuploidy.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the claimed methods are broadly drawn to an *in vitro* method for screening human subjects for the presence of a persistent transforming infection with HPV and an *in vitro* method for screening human subjects for the presence of any type of cellular changes characterized by enlarged cell nuclei and aneuploidy based on the detection of transcripts encoding a full-length HPV E6 protein in a test sample obtained from the human subject. As discussed above, the claimed methods are associated with a high degree of unpredictability. Despite the breadth of the claims and the inherent unpredictability associated with the claimed methods, the specification provides only minimal guidance regarding practice of the full scope of the claimed methods and provides no evidence to establish that the presence of transcripts encoding full-length E6 proteins from HPV types other than HPV-16, 18, 31, 33, and 45 is associated with a human subject's risk of developing a persistent HPV infection or having cells exhibiting aneuploidy and enlarged nuclei. As noted above, these aspects of the claimed methods are also not described in the prior art. Finally, the quantity of experimentation required to practice the full scope of the claimed methods is immense. Thus, given the broad claims in an unpredictable art, the large quantity of unpredictable experimentation required to

practice the full scope of the claimed methods, the minimal guidance provided in the specification, the limitations of the working examples, and the negative teachings in the art, balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to successfully practice the claimed methods.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 9, 10, 14, 18, 19, 23, 27, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 10, 14, 19, 23, and 28 are vague and indefinite, because the exemplary language in these claims renders the metes and bounds of the claims unclear. Claims 5, 14 and 23 recite that the method must be capable of detecting E6/E7 mRNA from HPV types 16, 18, 31, 33, *and preferably 45*. Claims 10, 19, and 28 require that the human subjects from which the tested cell or tissue samples are obtained have been previously identified as being infected with HPV DNA, *preferably in the cell or tissue under test*. It is not clear whether the italicized exemplary language in claims 5, 10, 14, 19, 23, and 28 is a required part of the claimed invention, and therefore, the metes and bounds of these claims are unclear. See also MPEP § 2173.05(d) for a further discussion of exemplary claim language.

Claims 9, 18, and 27 contain the trademark/trade name Pre-Tect HPV-Proofer Test. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a particular type of assay kit and method for detecting HPV and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-6, 10, 11, 13-15, 19, 20, 22-24, 28, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakagawa et al. (Journal of Medical Virology (2000) 62: 251-256; cited previously).

Claims 1, 4-6, 10, and 11 are drawn to an *in vitro* method for screening human subjects for the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at

least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of an HPV that encode full-length E6 protein in a cell or tissue sample obtained from the subject. Claims 2, 13-15, 19, and 20 are drawn to a method for screening human subjects for the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of an HPV that encode full-length E6 protein in a cell or tissue sample obtained from the subject. Claims 3, 22-24, 28, and 29 are drawn to a method for screening human subjects for the presence of a persistent transforming infection with HPV in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from the subject..

Regarding claims 1-3, Nakagawa teaches an *in vitro* method that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from a human subject (see pages 252-254). Thus, the method of Nakagawa results in "detecting the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at least one cell or tissue obtained from a human subject", "detecting the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue obtained from a human subject", and "detecting the presence of a persistent transforming infection with HPV in at least one cell or tissue obtained from a human subject" as required by claims 1-3, respectively.

Regarding claims 4-6, 13-15, and 22-24, the method of Nakagawa comprises detecting the presence of mRNA transcripts of the HPV E6/E7 gene using a technique that is able to detect

HPV-16, 18, 31, 33, and 45 (see page 253). Also, the method of Nakagawa comprises detecting the expression of mRNA transcripts from HPV-16, 18, 31, 33, and 45 (pages 253-254).

Regarding claims 10, 11, 19, 20, 28, and 29, in the methods of Nakagawa, the human subjects from which the cell and tissue samples are obtained have been previously identified as being infected with HPV in the cell or tissue under test (page 252). Also, the human subjects screened in the method of Nakagawa have a previous diagnosis of CIN 1 (page 252).

9. Claims 1-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Karlsen (WO 2003/057914 A2; cited on an IDS).

Claims 1 and 4-12 are drawn to an *in vitro* method for screening human subjects for the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of an HPV that encode full-length E6 protein in a cell or tissue sample obtained from the subject. Claims 2 and 13-21 are drawn to a method for screening human subjects for the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of an HPV that encode full-length E6 protein in a cell or tissue sample obtained from the subject. Claims 3 and 22-30 are drawn to a method for screening human subjects for the presence of a persistent transforming infection with HPV in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from the subject..

Regarding claims 1-3, Karlsen teaches an *in vitro* method that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from a human subject (see, for example, page 6, line 10 - page 7, line 15, page 21, line 5 – page 23, line 25, and page 25, line 22 - page 26, line 11). Thus, the method of Karlsen results in "detecting the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at least one cell or tissue obtained from a human subject", "detecting the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue obtained from a human subject", and "detecting the presence of a persistent transforming infection with HPV in at least one cell or tissue obtained from a human subject" as required by claims 1-3, respectively. It is also noted that Karlsen expressly teaches applying the disclosed methods to detecting the presence of HPV in a cell or tissue sample obtained from a human subject, screening a cell or tissue sample obtained from a human subject for cellular abnormalities characterized by aneuploidy and enlarged cell nuclei, and screening human subjects for a persistent transforming HPV infection (see, for example, page 6, line 10 – page 8, line 35, page 11, line 9 – page 12, line 31, and pages 14-18).

Regarding claims 4-6, 13-15, and 22-24, the method of Karlsen comprises detecting the presence of mRNA transcripts of the HPV E6/E7 gene using a technique that is able to detect HPV-16, 18, 31, 33, and 45 (see, for example, page 19, lines 14-17 and page 21, lines 5-24). Also, the method of Karlsen comprises detecting the expression of mRNA transcripts from HPV-16, 18, 31, 33, and 45 (see, for example, page 19, lines 14-17 and page 21, lines 5-24).

Regarding claims 7-9, 16-18, 25-27, Karlsen teaches detecting the expression of mRNA transcripts of the E6/E7 gene using real-time NASBA (see, for example, page 18, line 30 – page 19, line 12 and page 26, line 23 – page 28, line 22). Karlsen also teaches that the Pre-tect HPV-Proofer assay kit can be used to detect the expression of mRNA transcripts of the E6/E7 gene using real-time NASBA (see pages 72-73, for example).

Regarding claims 10, 11, 19, 20, 28, and 29, in the methods of Karlsen, the human subjects from which the cell and tissue samples are obtained have been previously identified as being infected with HPV in the cell or tissue under test (see, for example, page 14, lines 3-5). Also, Karlsen teaches that the human subjects screened by the disclosed methods have a previous diagnosis of CIN 1 lesions, ASCUS, or condyloma (see, for example, page 14, line 3 - page 15, line 16, page 16, line 26 - page 17, line 7, and page 19, lines 33-36).

Regarding claims 12, 21, and 30, Karlsen teaches applying the disclosed methods to primary screening of individuals who have no previous cytology-based diagnosis of cervical abnormalities (see, for example, page 7, lines 15-24, page 9, lines 6-16).

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 7,553,623 in view of Karlsen (WO 2003/057914 A2; cited on an IDS).

The instant claims 1 and 4-12 are drawn to an *in vitro* method for screening human subjects for the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of an HPV that encode full-length E6 protein in a cell or tissue sample obtained from the subject. The instant claims 2 and 13-21 are drawn to a method for screening human subjects for the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of an HPV that encode full-length E6 protein in a cell or tissue sample obtained from the subject. The instant claims 3 and 22-30 are drawn to a method for screening human subjects for the presence of a persistent transforming infection with HPV in at least one cell or tissue that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from the subject..

Claims 1-9 of the '623 patent recite a method for screening human subjects to assess their risk of developing cervical carcinoma that comprises using a method, such as real-time NASBA, to detect the expression of E6 mRNA transcripts in a sample obtained from the subject. The claims of the '623 patent also recite that the method is used to detect the expression of E6 mRNA transcripts from HPV-16, 18, 31, 33, and 45 in samples obtained from human subjects having a previous diagnosis of HPV infection, CIN-1 lesions, ASCUS, or condyloma.

The claims of the '623 patent do not explicitly state that full-length E6 mRNA transcripts are detected in the disclosed methods as required by the instant claims 1-30. Also, the claims of the '623 patent do not teach using the Pre-tect HPV-Proofer assay kit to detect full-length E6 mRNA transcripts as required by the instant claims 9, 18, and 27. Finally, the claims of the '623 patent do not teach using the method to screen human subjects lacking a cytology-based diagnosis of cervical abnormalities as required by the instant claims 12, 21, and 30.

However, Karlsen teaches an *in vitro* method that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from a human subject (see, for example, page 6, line 10 - page 7, line 15, page 21, line 5 – page 23, line 25, and page 25, line 22 - page 26, line 11). Karlsen expressly teaches that the disclosed methods are useful for detecting the presence of HPV in a cell or tissue sample obtained from a human subject and screening human subjects for cervical cancer, which is a persistent transforming HPV infection characterized by cellular aneuploidy and enlarged cell nuclei (see, for example, page 6, line 10 – page 8, line 35, page 11, line 9 – page 12, line 31, and pages 14-18). Karlsen also teaches that the Pre-tect HPV-Proofer assay kit can be used to detect the expression of mRNA transcripts of the E6/E7 gene using real-

time NASBA (see pages 72-73, for example), and that the disclosed methods may be applied to the primary screening of individuals who have no previous cytology-based diagnosis of cervical abnormalities (see, for example, page 7, lines 15-24, page 9, lines 6-16).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to detect transcripts encoding a full-length E6 protein when practicing the methods recited in the claims of the '623 patent. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Karlsen taught that such transcripts were useful for detecting the presence of HPV in a cell or tissue sample obtained from a human subject and screening human subjects for cervical cancer, which is a persistent transforming HPV infection characterized by cellular aneuploidy and enlarged cell nuclei (see above). It is noted that detecting transcripts encoding a full-length E6 protein inherently results in "detecting the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at least one cell or tissue obtained from a human subject", "detecting the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue obtained from a human subject", and "detecting the presence of a persistent transforming infection with HPV in at least one cell or tissue obtained from a human subject" as required by claims 1-3, respectively. An ordinary artisan also would have been motivated to select any known means for performing real-time NASBA when practicing the methods recited in the claims of the '623 patent, such as the Pre-Tect HPV-Proofer assay kit taught by Karlsen, recognizing its suitability for the intended purpose. As noted in MPEP 2144.07, it is *prima facie* obvious to select a known material or method based on its suitability for the intended purpose in

the absence of unexpected results. Finally, an ordinary artisan would have been motivated to apply the methods recited in the claims of the '623 patent to primary screening of human subjects lacking a cytological diagnosis of cervical abnormalities, since Karlsen taught that this was a suitable use for a method of screening human subjects comprising the detection of full-length E6 mRNA transcripts. Thus, the instant claims 1-30 are an obvious variant of claims 1-9 of the '623 patent in view of Karlsen.

12. Claims 1-4, 6-8, 10, 11, 13, 15-17, 19, 20, 22, 24-26, 28, and 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 12/483,860. Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 1-14 of the '860 application recite all of the limitations of the instant claims 1-4, 6-8, 10, 11, 13, 15-17, 19, 20, 22, 24-26, 28, and 29. It is noted that, since the claims of the '860 application teach detecting full-length HPV E6 mRNA transcripts, practice of the methods recited in the claims of the '860 application inherently results in "detecting the presence of HPV that exhibits a loss of regulation of E6/E7 mRNA expression and a loss of replication and/or expresses a stabilized pre-mRNA that encodes a full-length E6 protein in at least one cell or tissue obtained from a human subject", "detecting the presence of cellular changes characterized by enlarged cell nuclei and aneuploidy in at least one cell or tissue obtained from a human subject", and "detecting the presence of a persistent transforming infection with HPV in at least one cell or tissue obtained from a human subject" as required by claims 1-3, respectively. Thus, the instant claims 1-4, 6-8, 10, 11, 13, 15-17, 19, 20, 22, 24-26, 28, and 29 are anticipated by claims 1-14 of the '860 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 5, 9, 12, 14, 18, 21, 23, 27, and 30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 12/483,860 in view of Karlsen et al. (WO 2003/057914 A2; cited on an IDS).

As discussed above, claims 1-14 of the '860 application anticipate the instant claims 1-4, 6-8, 10, 11, 13, 15-17, 19, 20, 22, 24-26, 28, and 29.

The claims of the '860 application do not teach that the method is capable of detecting full-length E6 mRNA transcripts from HPV-16, 18, 31, 33, and 45 as required by claims 5, 14, and 23. The claims of the '860 application also do not teach that the detection of the full-length E6 mRNA transcripts is conducted using the Pre-tect HPV-Proofer assay kit as required by claims 9, 18, and 27. Finally, the claims of the '860 application do not teach using the method to screen human subjects lacking a cytology-based diagnosis of cervical abnormalities as required by claims 12, 21, and 30.

However, Karlsen teaches an *in vitro* method that comprises detecting the presence of mRNA transcripts of the E6/E7 gene of a human papillomavirus that encode full-length E6 protein in a cell or tissue sample obtained from a human subject (see, for example, page 6, line 10 - page 7, line 15, page 21, line 5 – page 23, line 25, and page 25, line 22 - page 26, line 11).

Regarding claims 5, 14, and 23, the method of Karlsen comprises detecting the presence of mRNA transcripts of the HPV E6/E7 gene using a technique that is able to detect HPV-16, 18,

31, 33, and 45 (see, for example, page 19, lines 14-17 and page 21, lines 5-24). Karlsen teaches that detecting E6 transcripts from these HPV types are "high-risk and cancer-associated HPV types" (page 21).

Regarding claims 9, 18, and 27, Karlsen teaches that the Pre-tect HPV Proofer assay kit is a means for performing a multiplexed real-time NASBA analysis of E6 mRNA transcripts (pages 72-73, for example).

Regarding claims 12, 21, and 30, Karlsen teaches applying the disclosed methods to primary screening of individuals who have no previous cytology-based diagnosis of cervical abnormalities (see, for example, page 7, lines 15-24, page 9, lines 6-16).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to modify the method recited in the claims of the '860 application such that it is capable of detecting full-length E6 mRNA transcripts from HPV-16, 18, 31, 33, and 45. Any ordinary artisan would have been motivated to do so, since Karlsen identified these types of HPV as "high-risk and cancer-associated" (see page 21). An ordinary artisan also would have been motivated to select any known means for performing real-time NASBA when practicing the methods recited in the claims of the '860 application, such as the Pre-Tect HPV-Proofer assay kit taught by Karlsen, recognizing its suitability for the intended purpose. As noted in MPEP 2144.07, it is *prima facie* obvious to select a known material or method based on its suitability for the intended purpose in the absence of unexpected results. Finally, the ordinary artisan would have been motivated to apply the methods recited in the claims of the '860 application to primary screening of human subjects lacking a cytological diagnosis of cervical abnormalities, since Karlsen taught that this was a suitable use for a method of detecting full-length E6 mRNA

transcripts. Thus, the instant claims 5, 9, 12, 14, 18, 21, 23, 27, and 30 are an obvious variant of claims 1-14 of the '860 application in view of Karlsen.

This is a provisional obviousness-type double patenting rejection.

Conclusion

14. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637